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A Meta-Analysis of Colorectal Cancer and Asbestos Exposure

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A meta-analysis of the relation between asbestos exposure and colorectal cancer mortality was conducted, using published reports of 20 asbestos-exposed cohorts. Summary standardized mortality ratios (SMRs) for colorectal cancer were examined in relation to asbestos type and estimates of dust exposure (as direct estimators of asbestos exposure) and in relation to lung cancer SMR and the proportion of all deaths due to mesothelioma (as proxy estimators of asbestos exposure). An elevated summary SMR was observed in cohorts exposed to amphibole asbestos (summary SMR = 1.47; 95% confidence interval (CI) 1.09–2.00), but not in cohorts exposed to serpentine asbestos (summary SMR = 1.04; 95% CI 0.81–1.33) or in cohorts exposed to both serpentine and amphibole asbestos (summary SMR = 1.03; 95% CI 0.74–1.42). Cohorts having a lung cancer SMR greater than 2.00 had a summary SMR of 1.51 (95% CI 1.29–1.76), and cohorts in which more than 1% of all deaths were attributed to mesothelioma had a summary SMR of 1.24 (95% CI 0.94–1.64). After stratifying the cohorts based on mortality due to all cancers excluding those known or suspected to be associated with asbestos exposure, lung cancer mortality was not clearly associated with colorectal cancer mortality, suggesting that the crude association between these factors may be due to misdiagnosis of lung cancer as other types of cancer in the reported causes of death. These results suggest that exposure to amphibole asbestos may be associated with colorectal cancer, but these findings may reflect an artifact of miscertification of cause of death. The results also suggest that serpentine asbestos is not associated with colorectal cancer. *Am J Epidemiol* 1994;139:1210–22.

asbestos; colonic neoplasms; meta-analysis; occupational diseases

The role of asbestos exposure in the etiology of colorectal cancer remains unclear despite several previous quantitative reviews of the literature (meta-analyses) (1–4). These have noted a slight overall elevation in mortality from colorectal neoplasms among cohorts of asbestos-exposed workers (summary standardized mortality ratios (SMRs) = 1.03–1.14). Some reviews, in attempting to identify sources of heterogeneity among cohorts, have focused upon factors that may serve as proxy indicators of asbestos exposure. Of these, lung cancer mortality is most prominent because a correlation between colorectal cancer mortality and lung cancer mortality has been consistently observed (2, 3, 5). The extent to which increasing lung cancer mortality corresponds to increasing intensity of asbestos exposure, however, has been disputed (6, 7), and the validity of using lung cancer mortality as a proxy estimator of asbestos ex-

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Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.

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posure has not been established, although it is intuitively attractive. No previous meta-analysis has investigated direct estimators of asbestos exposure, such as type of asbestos or dust levels, as sources of heterogeneity in colorectal cancer SMRs. Previous meta-analyses also have differed on whether they distinguished between mortality and incidence endpoints and on the statistical methods used.

This report presents a meta-analysis of asbestos exposure and colorectal cancer mortality in which asbestos type and dust levels are investigated as direct estimators of asbestos exposure. Mortality from lung cancer and the proportion of deaths due to mesothelioma are investigated as proxy estimators of asbestos exposure. Two statistical methods, Poisson regression and an approach based on random effects, are used to compute summary SMRs and confidence intervals. The results and inferences obtained from these methods are compared and contrasted.

MATERIALS AND METHODS

Cohorts included in analysis

A search of the literature was performed to find all published reports of asbestos-exposed cohorts in which mortality due to cancers of the colon and rectum was reported. From 16 studies identified (8–23), the following data regarding 20 cohorts were abstracted: observed and expected numbers of deaths due to colon and rectal cancer (or colorectal cancer), lung cancer, esophageal cancer, stomach cancer, all cancers, and all causes of death; the total number of reported mesotheliomas; whether a latency period was considered and, if so, the length of that period; the types of asbestos to which cohort members were exposed; and information regarding dust exposure. When results were presented using both death certificate and "best evidence" criteria, results based upon death certificates were used. When a study presented results both ignoring latency and taking a latency period into account, the latter results were used. The most recent report for any given cohort was used.

From the abstracted data, SMRs were computed for each cohort for the following diseases: colorectal cancer; lung cancer; all cancers; all cancers after subtracting colorectal cancers, lung cancers, mesotheliomas, esophageal cancers, and stomach cancers; and all deaths. In addition, the percentage of all deaths due to mesotheliomas in each cohort was computed. These measures are listed in table 1. For one study (16) in which the deaths due to all cancers were not reported, this number was estimated from general population rates (24).

Cohorts were classified on asbestos type based upon the types used, the proportions in which they were used, and the time periods during which they were used. If a particular type constituted 95 percent or more of asbestos exposure, it was considered to be the predominant exposure for the cohort. In cohorts for which quantitative information on the composition of asbestos exposure was not available, a best judgment regarding classification on type was made. Three categories of asbestos type were defined: 1) exposure entirely or predominantly serpentine asbestos (chrysotile), 2) exposure entirely or predominantly amphibole asbestos (amosite, crocidolite), and 3) exposure to both serpentine and amphibole asbestos, with proportions unknown. For simplicity, these categories will be referred to as serpentine, amphibole, and mixed, respectively, throughout the text. Information regarding the type of asbestos was not reported for three cohorts. Two of these cohorts were derived from a German nationwide registry of asbestos workers (18), for which the exposure was assumed to be mixed. The other cohort (8) also was coded as mixed asbestos type based on other published materials (25).

A measure of typical dust exposure (mean, median, or range) was obtained for each cohort, either by abstracting a directly reported value or by calculating an estimate using published information. Based upon the distribution of these measures, the cohorts were placed into categories defined as low (<6 fibers/ml), moderate (6–12 fibers/ml), or high (>12 fibers/ml) exposure. For

TABLE 1. Cohorts reporting the standardized mortality ratio for colorectal cancer and asbestos exposure, with epidemiologic characteristics for asbestos-related cancers

Study and year	Cohort		Colorectal cancer		Lung cancer		Other cancers*		All causes		No. of mesotheliomas	% of all deaths from mesothelioma
	Size (no.)	Sex	O/E†	SMR†	O/E	SMR	O/E	SMR	O/E	SMR		
Puntoni et al., 1977 (8)‡	4,274	M†	34/22.23	1.53	123/33.94	3.62	108/80.63	1.34	1,070/777.47	1.38	0	0.00
Selikoff et al., 1979 (9)	17,800	M	54/34.00	1.59	397/93.70	4.24	359/130.20	2.76	1,946/1,376.00	1.41	101	5.20
McDonald et al., 1980 (10)	10,939	M	79/101.00	0.78	230/184.00	1.25	320/300.84	1.06	3,291/3,019.30	1.09	10	0.30
Acheson et al., 1984 (11)	5,969	M	10/7.60	1.32	57/29.10	1.96	33/28.20	1.17	333/298.80	1.11	5	1.50
Ohlson et al., 1984 (12)	3,297	M	15/20.90	0.72	27/25.70	1.05	72/68.30	1.05	586/727.00	0.81	5	0.85
Ohlson and Hogstedt, 1985 (13)	1,176	M	11/5.90	1.86	11/9.00	1.22	21/29.20	0.72	220/214.00	1.03	0§	0.00
Peto et al., 1985 (14)												
Cohort I	145	M	3/2.07	1.45	20/5.55	3.60	13/5.13	2.53	123/67.90	1.81	7	5.70
Cohort II	283	F†	4/2.02	1.98	4/1.90	2.11	9/11.01	0.82	49/49.38	0.99	0	0.00
Cohort III	3,211	M	20/26.72	0.75	132/100.45	1.31	68/82.30	0.83	1,113/972.94	1.14	11	0.99
Gardner et al., 1986 (15)	1,510	M	11/15.40	0.71	41/42.20	0.97	53/56.20	0.94	486/519.00	0.94	1	0.21
	657	F										
Hodgson and Jones, 1986 (16)	31,150	M	14/27.40	0.51	152/112.10	1.36	98/155.10	0.63	834/931.60	0.90	34	4.08
Seidman et al., 1986 (17)	933	M	22/11.90	1.85	102/20.51	4.97	61/33.94	1.80	593/355.87	1.67	6	1.01
Woitowitz et al., 1986 (18)												
Cohort I	2,752	M	5/6.34	0.79	22/15.29	1.44	18/21.21	0.85	185/194.67	0.95	6	3.24
	318	F										
Cohort II	398	M	3/1.39	2.16	9/2.60	3.46	8/4.94	1.62	71/40.69	1.74	3	4.23
	267	F										
Enterline et al., 1987 (19)	1,074	M	23/19.90	1.16	77/28.44	2.71	84/67.49	1.24	944/762.77	1.24	8	0.85
Hughes et al., 1987 (20)												
Cohort I	2,565	M	10/8.30	1.20	48/41.20	1.17	56/51.90	1.08	477/522.20	0.91	1	0.21
Cohort II	4,366	M	11/15.00	0.73	107/74.30	1.44	86/89.90	0.96	874/922.70	0.95	7	0.80
Armstrong et al., 1988 (21)	6,505	M	14/12.28	1.14	91/34.47	2.64	81/54.33	1.49	820/535.95	1.53	33	4.02
Piolatto et al., 1990 (22)	1,058	M	6/6.60	0.91	22/19.90	1.11	42/37.00	1.14	427/286.30	1.49	2	0.47
Albin et al., 1990 (23)	1,929	M	26/20.14	1.29	35/20.14	1.74	80/52.39	1.53	592/562.04	1.05	13	2.20

* All cancers excluding colorectal cancer, lung cancer, mesothelioma, esophageal cancer, and stomach cancer.
† O, observed number; E, expected number; SMR, standardized mortality ratio; M, male; F, female.
‡ Numbers in parentheses, reference.
§ C-G. Ohlson, Örebro Medical Center Hospital, personal communication, 1991.

converting particle counts to fiber counts, 1,000,000 particles/cu ft were considered approximately equal to 35.3 particles/ml, which was considered approximately equal to one fiber/ml (5). Because concentrations of respirable particulates usually follow a distribution that is unimodal and positively skewed (25), median values would be expected to be smaller than mean values. In the cases where ranges were defined, a judgment was made based upon the characteristics of the cohort regarding which dust level category best represented typical exposure. Four cohorts (8, 16, 18) for which it was not possible to obtain a typical dust exposure were placed into a fourth category, dust level undetermined, for analysis. Type of asbestos and dust exposure classifications for the cohorts are listed in table 2.

Latency was considered because cancer attributable to asbestos exposure typically does not occur until some time has passed after exposure; this period has been estimated at 5–35 years for lung cancer and as long as 50 years for mesothelioma (5). For the studies that reported results based on a latency period, latency periods were defined as the time elapsed since the first exposure. For this analysis, studies were categorized simply on whether they had considered a latency period, rather than on the length of the latency period used. Latency periods for each cohort are presented in table 2.

Statistical analyses

Analyses were performed separately for SMR studies with exclusively male cohorts and for all SMR studies combined. However, only one small cohort was exclusively female (14), and females represented a small percentage of the overall membership of all cohorts. Since the results for males alone were not appreciably different from the results for all cohorts, results based on analyses using all cohorts are presented.

Two methods were used to obtain summary SMRs and 95 percent confidence intervals (CIs) for univariate analyses: 1) Poisson regression techniques and 2) a technique based upon random effects assumptions.

Poisson regression. Summary SMRs and 95 percent confidence intervals were obtained from multiplicative Poisson regression models (26). The goodness of fit for a model is evaluated by the deviance statistic, which has a chi-squared distribution with degrees of freedom equal to the number of cohorts minus the total number of terms in the model (27). A model fitting the data well would have an expected deviance statistic equal to the degrees of freedom. Summary SMRs based upon Poisson regression models will be identical to those obtained from elementary summation methods that were used in earlier quantitative reviews of asbestos exposure and colorectal cancer (1, 4). Confidence intervals for summary SMRs from Poisson regression are obtained by exponentiating the confidence intervals for the linear predictor, which are calculated from the variance-covariance matrix of the parameter estimates. This method of obtaining confidence intervals has been illustrated in detail for logistic regression (28), but the calculation for Poisson regression will be analogous.

Random effects method. This approach for computing summary SMRs is adapted from a method for combining event rate differences from clinical trials (29) and is described in the report by Frumkin and Berlin (2). This method allows for heterogeneity among study results that may remain even after categorizing studies into relatively homogeneous groups. For k studies, a chi-squared statistic (Q) for heterogeneity with $k - 1$ degrees of freedom can be computed to test the null hypothesis that the studies are homogeneous, i.e., measuring the same underlying SMR. However, even if significant heterogeneity is found, the estimation method is still valid since any heterogeneity is built into the variance of the summary SMR. The summary SMR for k studies is obtained by exponentiating the weighted mean of the reported log SMRs. An approximate 95 percent confidence interval for the summary SMR can be obtained by expo-

TABLE 2. Classification of types of asbestos and dust levels to which cohorts were exposed and years of latency taken into account

Study and year	Description of types of asbestos	Asbestos type code*	Typical quantitative dust level	Dust level code†	Latency (years)
Puntoni et al., 1977 (8)‡	Reported as mixed in reference 25	Mixed§	Not reported	NA	0
Selikoff et al., 1979 (9)	Chrysotile only to 1943; chrysotile and amosite after 1943	Mixed§	Mean = 4–12 fibers/ml	Moderate	20
McDonald et al., 1980 (10)	Chrysotile	Serpentine§	Mean = 19 mppcf‖	High	20
Acheson et al., 1984 (11)	Mainly amosite; <3% chrysotile, 1946–1973; very brief use of crocidolite	Amphibole§	30 fibers/ml most of study	High	0
Ohlson et al., 1984 (12)	Chrysotile, crocidolite, amosite	Mixed	Mean = 3–5 fibers/ml	Low	20
Ohlson and Hogstedt, 1984 (13)	Mainly chrysotile; <1% amosite and crocidolite	Serpentine§	Median < 2 fibers/ml	Low	0
Peto et al., 1985 (14)					
Cohort I	Mainly chrysotile; 5% crocidolite, 1932–1969	Serpentine§	Range = 6.6–13.1 fibers/ml	Moderate	0
Cohort II	Mainly chrysotile; 5% crocidolite, 1932–1969	Serpentine§	Range = 2.8–11.1 fibers/ml	Moderate	0
Cohort III	Mainly chrysotile; 5% crocidolite, 1932–1969	Serpentine§	Range = 0.8–6.2 fibers/ml	Moderate	0
Gardner et al., 1986 (15)	Chrysotile	Serpentine	Mean < 1 fiber/ml since 1970	Low	0
Hodgson and Jones, 1986 (16)	Not reported; national sample	Mixed	Not reported	NA	10
Seidman et al., 1986 (17)	Amosite	Amphibole	Median = 50 fibers/ml	High	5
Woitowitz et al., 1986 (18)					
Cohort I	Not reported; national sample	Mixed	Not reported	NA	9
Cohort II	Not reported; national sample	Mixed	Not reported	NA	9
Enterline et al., 1987 (19)	Chrysotile, amosite, crocidolite	Mixed	Mean = 10 mppcf	Moderate	0
Hughes et al., 1987 (20)					
Cohort I	Mainly chrysotile; some amosite and crocidolite	Serpentine§	Mean = 8.2 mppcf	Moderate	20
Cohort II	Mainly chrysotile; steady use of crocidolite	Mixed§	Mean = 7.7 mppcf	Moderate	20
Armstrong et al., 1988 (21)	Crocidolite	Amphibole	Median = 18 fibers/ml	High	0
Piolatto et al., 1990 (22)	Chrysotile	Serpentine§	Range = <4.5–13.1 fibers/ml	Moderate	0
Albin et al., 1990 (23)	Mostly chrysotile	Serpentine	Mean = 1.2 fibers/ml	Low	20

* Type codes: serpentine, mostly or all serpentine asbestos; amphibole, mostly or all amphibole asbestos; mixed, both serpentine and amphibole asbestos, proportions unknown.

† Dust level codes: low, dust exposure < 6 fibers/ml; moderate, dust exposure was 6–15 fibers/ml, high, dust exposure > 15 fibers/ml; NA, dust exposure information unavailable or could not be estimated.

‡ Numbers in parentheses, reference.

§ As listed in reference 25, pp. 6–20 to 6–21.

‖ mppcf, million particles per cubic foot of air; 1 mppcf ~ 35.3 particles/ml ~ 1 fiber/ml (5).

nentiating the endpoints for the 95 percent confidence interval for the log summary SMR (2).

Analysis strategy. Univariate analyses were performed using both the Poisson regression and random effects methods. For the random effects method, separate summary SMRs were calculated within each level of the categorical variable of interest. For Poisson regression, each variable was entered separately into a single-variable model. The random effects method is more appropriate than Poisson regression since there is likely to be heterogeneity in the cohorts within strata. Both methods are presented for comparison since Poisson regression provides the same summary SMRs as the summation methods that have been routinely used.

Lung cancer SMR was analyzed as a dichotomous variable, with categories defined as lung cancer SMR either less than or equal to 2.00 versus greater than 2.00. Lung cancer SMR also was analyzed in its continuous form using Poisson regression; summary SMRs were computed for a range of values bounded by the largest and smallest observed values of the lung cancer SMR. The percentage of all deaths attributed to mesothelioma was analyzed in a manner analogous to that for lung cancer SMR. The categories for the dichotomous form of this variable were defined as either less than or equal to 1 percent versus greater than 1 percent, with the cutpoint chosen to achieve roughly equal numbers of cohorts in both categories. Asbestos type and asbestos dust level were analyzed as categorical variables, as given in table 2.

Summary SMRs also were calculated within each level of asbestos type for lung cancer SMR, the percentage of all deaths due to mesothelioma, and dust level using the random effects method. Within-strata analyses also were performed after categorizing studies on whether or not they took a latency period into account.

Summary SMRs for all variables also were computed using the random effects method after categorizing the studies based on the SMR for all cancers, excluding those types known or suspected to be related to asbestos exposure (lung, mesothelioma, esophageal, stomach, and colorectal cancers). The studies were divided into two strata, using the median SMR of 1.11 as the dividing point. This analysis was performed to investigate the hypothesis of Doll and Peto (5) that the observed association between lung cancer SMRs and colorectal cancer SMRs may, in fact, be due to miscertification on death certificates of lung cancer and mesothelioma as cancer of other types. Other cancers have been implicated with asbestos exposure, namely, cancers of the oral cavity, larynx, and kidney (5, 9, 30). As these neoplasms were inconsistently reported across the cohorts used, they were not included with cancers associated with asbestos exposure. The other cancer SMR thus could be biased upward; however, as these cancers are less common than the other asbestos-related neoplasms (31), it is unlikely that this bias would cause an appreciable change in the categorization of cohorts on other cancer SMR.

The coding of dust level and asbestos type was based on the reported values from each paper, which were not always specific or complete, and thus presented the potential for misclassification. To evaluate the performance of these variables, we assessed their ability to predict lung cancer SMR and the percentage of all deaths attributed to mesotheliomas. If these variables performed in the expected manner, the occurrence of both lung cancer and mesothelioma would be expected to increase as the level of dust increases; in addition, cohorts exposed to amphibole asbestos would be expected to have higher levels of lung cancer and mesothelioma, as amphibole asbestos is considered more carcinogenic than is serpentine asbestos (5). The ability of these variables to predict lung cancer SMR was assessed by computing summary SMRs using the random effects method. The ability of the variables to predict mesothelioma occurrence was assessed by comparing the distribution of the percentage of all deaths attributed to me-

sothelioma for each level of the type of asbestos and dust exposure variables; differences between the strata for each variable were tested using the Kruskal-Wallis test (32).

The Statistical Analysis System (SAS) was used for obtaining descriptive statistics and for computing Kruskal-Wallis tests (33–35). Epilog Plus (36) was used to perform Poisson regression.

RESULTS

Assessment of dust level and asbestos type as predictors of lung cancer risk

The dust level variable predicted lung cancer SMRs in the expected direction. The summary lung cancer SMRs (with 95 percent CIs) were as follows: low dust exposure, 1.21 (0.90–1.63); moderate, 1.95 (1.22–3.12); high, 2.38 (1.24–4.56); and unknown, 2.19 (1.16–4.13). For the analysis of asbestos type, summary SMRs for lung cancer were as follows: serpentine asbestos, 1.40 (1.15–1.69); mixed asbestos, 2.13 (1.40–3.24); and amphibole asbestos, 2.97 (1.73–5.09).

The directions of effect for dust level and asbestos type on the percentage of all deaths due to mesothelioma were generally consistent with expectations, although none of these differences were statistically significant. For dust level, the median percentages of mesotheliomas were 0.53, 0.82, 1.25, and 3.65 for low, medium, high, and unknown dust levels, respectively (Kruskal-Wallis $\chi^2 = 1.96$ (3 df); $p = 0.58$). For asbestos type, the median percentages of mesotheliomas were 0.30, 2.04, and 1.50 among serpentine-, mixed-, and amphibole-exposed cohorts, respectively (Kruskal-Wallis $\chi^2 = 3.80$ (2 df); $p = 0.15$). Thus, based on observing the expected relations between dust levels and lung cancer SMR, asbestos type and lung cancer SMR, dust levels and the proportion of deaths due to mesotheliomas, and asbestos type and the proportion of deaths due to mesothelioma, we feel that the categorizations by dust level and asbestos type represent exposure meaningfully.

Meta-analysis results

Table 3 presents univariate results based upon all SMR studies for the direct estimators of asbestos exposure (asbestos type and dust level) and for the proxy estimators (lung cancer SMR and the percentage of deaths due to mesothelioma). In general, the random effects method and the Poisson regressions gave similar estimates of the summary colorectal cancer SMR, but the random effects method tended, appropriately, to produce wider confidence intervals when the SMRs were heterogeneous across studies.

Overall, a slight elevation in the summary colorectal cancer SMR was observed (SMR = 1.10 for random effects and 1.02 for Poisson regression) with considerable heterogeneity remaining. The summary colorectal cancer SMR was elevated in cohorts in which the lung cancer SMR was greater than 2.00, with both methods giving similar SMRs (1.51 and 1.48) and confidence intervals; these studies were relatively homogeneous. Slightly elevated summary colorectal cancer SMRs (1.24 and 1.23) were observed for cohorts in which mesotheliomas comprised more than 1 percent of all deaths. The random effects method gave broader confidence intervals (including the null value of 1.00) than did Poisson regression, which reflected the relatively large heterogeneity remaining in the data.

Cohorts exposed to amphibole asbestos had an elevated summary colorectal cancer SMR, with both methods providing similar SMRs (1.47 and 1.45) and confidence intervals. No appreciable elevation of the summary colorectal cancer SMR was observed for cohorts exposed to either serpentine asbestos or mixed asbestos. The summary SMR increased as the dust level increased under the random effects model, but showed no clear pattern under the Poisson regression model. All categories of dust level displayed considerable heterogeneity.

The results obtained within categories of asbestos type are presented in table 4. The summary SMR for colorectal cancer was el-

TABLE 3. Summary colorectal cancer standardized mortality ratios (SMRs) calculated from random effects and Poisson regression

Study characteristic	Random effects					Poisson regression				
	No. of studies	Colorectal cancer		Heterogeneity χ^2	p value	Colorectal cancer		Model df	Deviance χ^2	p value
		SMR	95% CI*			SMR	95% CI			
Overall	20	1.10	0.92–1.32	51.83	<0.001	1.02	0.92–1.13	19	51.84	<0.001
Lung cancer SMR										
Dichotomous										
≤2.00	12	0.89	0.73–1.09	19.89	0.056	0.83	0.73–0.95			
								18	22.86	0.20
>2.00	8	1.51	1.29–1.76	4.47	0.83	1.48	1.27–1.74			
Continuous										
0.97 (minimum)		NA*				0.77	0.67–0.89			
1.00		NA				0.78	0.67–0.90			
2.00		NA				0.98	0.88–1.09			
								18	18.25	0.44
3.00		NA				1.23	1.10–1.38			
4.00		NA				1.55	1.32–1.82			
4.97 (maximum)		NA				1.94	1.55–2.42			
% of all deaths from mesotheliomas										
Dichotomous										
≤1	11	1.01	0.80–1.26	23.23	0.0079	0.92	0.81–1.05			
								18	44.45	<0.001
>1	9	1.24	0.94–1.64	19.35	0.011	1.23	1.05–1.44			
Continuous										
0 (minimum)		NA				0.94	0.82–1.08			
0.5		NA				0.97	0.86–1.09			
1.0		NA				0.99	0.89–1.10			
								18	48.85	<0.001
3.0		NA				1.10	0.97–1.24			
5.0		NA				1.21	0.98–1.50			
5.7 (maximum)		NA				1.26	0.98–1.61			
Asbestos type										
Serpentine	9	1.04	0.81–1.33	15.72	0.057	0.90	0.78–1.05			
Mixed	8	1.03	0.74–1.42	24.98	<0.001	1.08	0.92–1.26	17	43.69	<0.001
Amphibole	3	1.47	1.09–2.00	2.18	0.59	1.45	1.08–1.93			
Dust level										
Low	4	1.06	0.69–1.62	8.49	0.049	1.01	0.79–1.29			
Medium	8	1.13	0.86–1.47	12.97	0.099	1.14	0.96–1.36			
								16	49.27	<0.001
High	4	1.18	0.75–1.86	14.06	<0.001	0.94	0.79–1.12			
Undetermined	4	1.02	0.52–2.02	13.83	0.0011	0.98	0.75–1.27			

* CI, confidence interval; NA, not applicable.

evated in cohorts that had a lung cancer SMR over 2.00 and that were exposed to serpentine asbestos or to mixed asbestos. Among amphibole-exposed cohorts, the summary SMR for colorectal cancer was elevated regardless of the level of the SMR for lung cancer. When the other exposure variables were examined, all three amphibole-exposed cohorts had greater than 1 percent of all deaths due to mesothelioma and had been exposed to high dust levels; these cohorts showed increased risk (summary colorectal cancer SMR = 1.47). Summary colorectal cancer SMRs were not clearly elevated in the serpentine or mixed exposure cohorts that had greater than 1 percent of deaths due to mesothelioma. Cohorts exposed to serpentine asbestos actually showed a pattern of decreasing colorectal cancer risk as dust exposure increased, while mixed asbestos cohorts showed no clear pattern.

TABLE 4. Analysis by asbestos type, with standardized mortality ratios (SMRs) and confidence intervals (CIs) obtained using the random effects method

Study characteristic	Asbestos type								
	Serpentine			Mixed			Amphibole		
	No. of studies	Colorectal cancer		No. of studies	Colorectal cancer		No. of studies	Colorectal cancer	
		SMR	95% CI		SMR	95% CI		SMR	95% CI
All studies	9	1.04	0.81–1.33	8	1.03	0.74–1.42	3	1.47	1.09–2.00
Lung cancer SMR									
≤2.00	7	0.99	0.76–1.28	4	0.66	0.49–0.88	1	1.32	0.71–2.45
>2.00	2	1.73	0.83–3.63	4	1.48	1.24–1.78	2	1.49	0.93–2.39
% of all deaths from mesothelioma									
≤1	7	0.98	0.74–1.30	4	1.03	0.71–1.49	0	NA*	
>1	2	1.31	0.91–1.88	4	1.04	0.52–2.11	3	1.47	1.09–2.00
Dust level									
Low	3	1.21	0.75–1.95	1	0.72	0.43–1.19	0	NA	
Medium	5	1.00	0.73–1.38	3	1.18	0.78–1.77	0	NA	
High	1	0.78	0.63–0.98	0	NA		3	1.47	1.09–2.00
Unknown	0	NA		4	1.03	0.52–2.02	0	NA	

* NA, not applicable.

Ten studies had reported results by latency, while 10 had not. These two groups were examined separately to determine if the results differed. There was no association between dust level and colorectal cancer SMR in either group of studies. In both groups, the colorectal cancer SMR was significantly elevated in those cohorts in which the lung cancer SMR was above 2.00 (no-latency cohorts: summary colorectal cancer SMR = 1.32, 95 percent CI 1.02–1.70; latency cohorts: summary colorectal cancer SMR = 1.67, 95 percent CI 1.25–2.21). The association between the percentage of deaths due to mesothelioma and colorectal cancer SMR was slightly stronger among studies in which a latency period was considered than among studies in which it was not considered. One study of amphibole-exposed subjects had taken a latency period into account (17) (colorectal cancer SMR = 1.85, 95 percent CI 1.22–2.81), while two had not (summary colorectal cancer SMR = 1.21, 95 percent CI 0.81–1.81). The smaller SMR for the latter studies perhaps reflects the influence of including subjects exposed to asbestos who had not experienced an adequate latency period for cancer to develop. Otherwise, there were no appreciable differences between studies that had reported findings by latency and those that had not.

Results obtained after dividing the cohorts based on the SMR for all cancers (excluding lung, mesothelial, esophageal, stomach, and colorectal cancers) are given in table 5. Among 10 cohorts in which the all cancer SMR was below 1.11, the summary colorectal cancer SMR was consistently low. Furthermore, no relation was indicated between the summary colorectal cancer SMR and dust level, asbestos type, or percentage of all deaths due to mesothelioma. The colorectal cancer SMR was elevated in the one study in which the lung cancer SMR was above 2.00. However, this cohort (14) was extremely small and the colorectal cancer SMR was unstable, being based on four deaths. These observations suggest that, in those studies in which all cancer mortality is low, the colorectal cancer risk is not related to asbestos exposure. However, it should be noted that there were no cohorts primarily exposed to amphibole asbestos in this group, and that most of the cohorts were in the low categories of lung cancer SMR and percentage of all deaths due to mesothelioma.

Among cohorts in which the all cancer SMR was greater than 1.11, the summary colorectal cancer SMR was uniformly elevated. These results are consistent with the view that asbestos exposure does not explain

TABLE 5. Colorectal cancer standardized mortality ratios (SMRs) by level of all other cancers,* with SMRs and confidence intervals (CIs) obtained using the random effects method

Study characteristic	SMR for other cancers ≤1.11			SMR for other cancers >1.11		
	No. of studies	Colorectal cancer		No. of studies	Colorectal cancer	
		SMR	95% CI		SMR	95% CI
Overall	10	0.85	0.68–1.06	10	1.43	1.25–1.65
Lung cancer SMR						
≤2.00	9	0.81	0.66–1.01	3	1.23	0.91–1.67
>2.00	1	1.98	0.74–5.28	7	1.50	1.28–1.75
% of all deaths from mesothelioma						
≤1	8	0.91	0.71–1.16	3	1.31	1.03–1.68
>1	2	0.57	0.37–0.90	7	1.50	1.26–1.77
Asbestos type						
Serpentine	6	1.00	0.73–1.37	3	1.23	0.88–1.71
Mixed	4	0.66	0.49–0.88	4	1.48	1.22–1.78
Amphibole	0	NA†		3	1.47	1.09–2.00
Asbestos dust level						
Low	3	0.98	0.53–1.80	1	1.29	0.88–1.90
Moderate	4	0.94	0.65–1.37	4	1.40	1.13–1.73
High	1	0.78	0.63–0.98	3	1.47	1.09–2.00
Unknown	2	0.57	0.37–0.90	2	1.57	1.14–2.17

* Cancers excluding lung cancer, mesothelioma, esophagus cancer, stomach cancer, and colorectal cancer.
† NA, not applicable.

elevated mortality from colorectal cancer in these studies (5). As all cohorts primarily exposed to amphibole asbestos were in the high category of all cancer SMR, an additional analysis was performed in this stratum dropping these cohorts. Little change in the summary colorectal cancer SMRs was found in categories containing amphibole-exposed cohorts, indicating that the three excluded cohorts were not exclusively elevating the summary SMRs within the stratum.

DISCUSSION

The results presented support the interpretation that, except perhaps among amphibole-exposed cohorts, the risk for colorectal cancer is not significantly elevated in asbestos-exposed cohorts. Univariate analyses indicated that elevated mortality from colorectal cancer was not related to dust level or to exposure to serpentine or mixed asbestos. The significant heterogeneity in the mixed asbestos category and the lack of specific data on the composition of asbestos exposure make inference in this category difficult. The estimates of dust exposure in the cohorts studied were necessarily crude and may have misclassified asbestos exposures; however, a clear gradient of lung cancer risk associated with dust level was observed that is consistent with a priori expectations.

The findings indicated that colorectal cancer risk is increased among amphibole-exposed cohorts. All three such cohorts had elevated risk, with a summary SMR of 1.47 (95 percent CI 1.09–2.00). In addition, several cohorts with mixed amphibole and serpentine exposure had significantly elevated SMRs for colorectal cancer. All cohorts primarily exposed to amphibole asbestos were in the high dust level category (table 4), so it was not possible to examine whether risk was a function of type and increasing dust level. However, within the high dust level category, there was only one other cohort (10) that was exposed to serpentine asbestos. This cohort was large (table 1) and took a 20-year latency period into account; colorectal cancer mortality was not elevated in this study. In contrast, only one amphibole-exposed cohort considered a latency period, a period of 5 years. Thus, the summary SMR for these cohorts may have been larger if longer latency periods had been taken into account. These observations support a role for amphibole asbestos in the etiology of

colorectal cancer. They also further reinforce that exposure to amphibole asbestos is more hazardous than is exposure to serpentine asbestos, although a recent report has indicated that the latter may be more harmful than once thought (37).

The mechanisms by which amphibole asbestos might cause colorectal cancer are not known. Migration of asbestos fibers into the colonic wall has been observed, indicating that exposure occurs to the epithelial cells from which carcinomas arise (38). Recently, both chrysotile and crocidolite asbestos were reported to produce aberrant crypt foci in the colon of rats (39). However, most animal studies have shown no evidence of carcinogenicity from lifetime ingestion of crocidolite (40), tremolite (41), or amosite (42) asbestos.

Previous studies have not used exposure estimates, but have used lung cancer SMR as a proxy estimator of asbestos exposure. The results presented here indicate that, although lung cancer SMR is correlated with colorectal cancer SMR, the interpretation of this association must be cautious as the colorectal cancer SMR is elevated only in those studies in which the SMR for all cancer, excluding asbestos-related cancer, is elevated. Indeed, after taking the SMR for all cancers into account, the association between lung cancer SMR and colorectal cancer SMR weakened appreciably. A similar phenomenon was observed for the percentage of all deaths from mesothelioma. The correlation between lung cancer SMR and colorectal cancer SMR (and the correlation between lung cancer SMR and all cancer SMR) has two alternative explanations (5). First, it suggests that, in studies of asbestos workers, lung cancer and mesothelioma are miscertified as cancers of all other sites. Since lung cancer may metastasize to nearly every organ system in the body (43) and since mesothelioma is underreported on death certificates (44), this hypothesis is plausible. The second explanation, that occupational exposure to asbestos may produce cancer in practically all organs, seems biologically implausible and is not supported by epidemiologic evidence to date.

An issue in any meta-analysis is whether the studies included are wholly representative of the literature. The present study is unlikely to suffer from this type of bias as the extensive literature on asbestos mortality has been the subject of multiple reviews (1–5, 25); these reviews were used to check the thoroughness of the literature search for this analysis. A related problem, publication bias, is more likely to exist because of negative findings regarding colorectal cancer mortality being less likely than positive findings to be published and thus not taken into account (45). Identified but not used were four studies that had incomplete information on one or more of the variables of interest, with no reasonable imputation possible (46–49).

Consistency of outcomes in a meta-analysis is important as different outcomes can be influenced by different factors; for a neoplasm with variable survival such as colorectal cancer, it is likely that the factors affecting incidence and mortality do not neatly overlap. Consequently, two cohort incidence studies (50, 51) and three proportional mortality studies (52–54) were excluded. However, an analysis was performed adding these five studies to the cohorts used, and no major changes in the inferences resulted.

Caution must be observed when interpreting the results of a meta-analysis of SMRs. The comparison of SMRs across studies is generally inappropriate unless the age structures of the populations generating the measures are equivalent (55). Although the bias that results from doing this generally will be small (56), it may be a significant source of heterogeneity. Summary measures also must be interpreted cautiously when there is evidence of meaningful underlying heterogeneity among the SMRs. When the heterogeneity statistics are large and very significant, they warn that considerable heterogeneity exists that should not be ignored.

The most important function of meta-analysis may be to identify sources of heterogeneity within a subject literature (56, 57). The findings presented here suggest

that asbestos type is an important source of heterogeneity and that the examination of this factor adds appreciably to the understanding of colorectal cancer risk.

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